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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,824	06/25/2001	Eric Perrier	11123.24US01	9749

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EXAMINER	
HANLEY, SUSAN MARIE	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 09/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,824	PERRIER ET AL.	
	Examiner	Art Unit	
	Susan Hanley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-78,82-87,91-93 and 95-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69-78,82-87,92,93 and 95-98* is/are rejected.

7)☒ Claim(s) *91* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed March 11, 2005 has been entered.

Claims 69-78, 82-87, 91-93 and 95-98 are pending.

Response to Arguments

Applicant's arguments with respect to claims 69-78, 82-87, 92-93 and 95-98 have been considered but are moot in view of the new ground(s) of rejection.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 73-75, 85 and 95-98 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 73 is rejected because the phrase the "field of lipolysis" is vague and indefinite. Lipolysis is a reaction that splits complex lipids into smaller lipids. It is unclear how a reaction is a "field." Does "field mean the study of the enzymes that carry out a such a reaction, the study of non-enzymatic reactions that carry out such a reaction, the study of how lipolysis relates to some thing or process, or does it have some other meaning? The metes and bounds of the phrase are undefined.

Claims 85, 95 and 97 are rejected because the term "particular" is vague and indefinite. It is unclear what "particular enzymatic assay" embodiment is preferred.

Claims 96 and 98 are rejected because they depend from claims that are not present.

Claim Rejections - 35 USC § 103

Claims 69, 87, 92 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable Comai et al. (US 4,218,443) in view of Halvorsen et al. (US 2001/0041708).

Comai et al. disclose a method for determining if polyether ionophores are suitable as anti-obesity or hypotriglyceride agents in warm blooded animals. Comai et al. teach an assay to determine the suitability of said agents by incubating lipoprotein lipase extracted from rat adipose tissue (col. 19, lines 48-52) with [C-14]-labelled and unlabelled substrate, glycerol trioleate, emulsified with lysophosphatidylcholine, fasted rat serum and bovine serum albumin. To this mixture was added the test agents and the free fatty acids were extracted and the radioactivity was counted (col. 20, lines 2-26). The inhibition constant for the agent was calculated. Comai et al. states that anti-obesity and hypotriglyeridemic affects are determined by *in vitro* or *in vivo* effects of fatty acid synthesis or lipolysis by pancreatic or lipoprotein lipase (col. 17, lines 17-23). This disclosure meets, in part, the indicated claims because the in vitro cell-free inhibition of LPL is used to evaluate the efficacy of inhibitors that can be used to treat obesity. The disclosure implicitly meets the limitation of the selection of an inhibitor for manufacture because Comai et al. intend the inhibitors as medical treatments. In order to accomplish this, the successful inhibitors would have to be made or manufactured.

Comai et al. do not teach that the successful inhibitor can be used in a topical composition, the testing of an extract of St. John's wort as a potential inhibitor for decreasing fat deposits which diminishes the "orange peel" appearance.

Halvorsen teaches that vegetable extracts such St. John's wort and other plat extract as can be tested for slimming activity (section 0008) and that such extracts can be formulated for topical use (section 0047).

Harland et al. disclose that fat stored in adipose triglycerides may be released by hydrolysis and that LPL and pancreatic lipase effect this hydrolysis (p. 2, section 0010, lines 1-2). Harland et al. also teach

that hepatic, LPL and pancreatic lipase share a high degree of primary sequence homology (p. 2, section 0015, lines 1-10).

Chapus discloses that the inhibition of pancreatic lipase inhibits, in part, the hydrolysis of dietary triglycerides which makes them non-absorbable by adipocytes (col. 3, lines 20-24).

It would have been obvious to one of ordinary skill in the art to employ the LPL assay taught by Comai et al. to test plant extracts such as St. John's wort which can be topically formulated for decreasing fat deposits and thus, diminishing the "orange peel" appearance. The ordinary artisan would have been motivated to do so because Comai et al. teach an *in vitro* cell free assay that is reliable for testing inhibitors of LPL. The ordinary artisan would have known from the disclosure by Harland et al. and Chapus that LPL, like pancreatic lipase, hydrolyze triglycerides, thus, causing the release and subsequent absorption of free fatty acids by adipocytes which leads to weight gain and cellulite accumulation (the orange peel effect). Therefore, the ordinary artisan would have had a reasonable expectation of success that the in vitro cell free LPL assay taught by Comai et al. could serve a test of inhibitors such as extracts of St. John's wort for decreasing fat deposits and the "orange peel" appearance because it was known at the time the invention was made that the activity of LPL is directly linked to the absorption of fatty acids by adipocytes and subsequence weight gain by mammals.

Claims 69-78 and 82-87, 92, 93, 95 and 97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cook et al. (US 5,855,917), Wagle et al. (US 6,326,396), Takahashi ct al. (US 5,955,072), Takeda et al. (US 5,244,798), Vainio et al. (1982), Cheng et al. (1990), Carroll et al. (1992), NEFA-C Kit instructions, Kikuchi et al. (US 4,301,244) and in further view of Pradines-Figueres et al. (1990) and Halvorsen et al. (US 2001/0041708).

Applicant argues that Cook et al. is directed to oral compositions to control body weight in animals and that Cook et al. do not disclose a screening assay but demonstrate inhibition of heparin-released LPL in preadipocytes. Applicant further argues that Cook et al. do not disclose a cell-free in

vitro screening method for identifying compounds and extracts for manufacturing of a topical composition for limiting the storage of triglycerides. Applicant argues that the secondary references do not overcome the deficiencies of Cook et al. because Wagle is directed to a different lipase, hormone sensitive lipase and Takanishi describes testing LPL is adipocytes. Applicant asserts that there is no motivation to combine Cook, Wagle and Takanishi with the addition references. Applicant argues that Takadea, Kikuchi and NEFA-C kit are directed to the analysis of free fatty acids in serum or plasma. Applicant argues that Bensadoun, Vainio, Cheng and Carroll are directed to in vitro studies of enzyme kinetics of LPL. Applicant argues that there is no reason to combine disparate references. Applicant argues that Halvorsen is does not teach cell-free in vitro testing, the Halvorsen is directed to decreasing lipogenesis by administrating linoleic acid and that said compound is tested against hormone sensitive lipase but not LPL, Halvorsen teaches assay methods using preadipocytes and that CLA compounds did not diminish lipolysis.

Applicant further asserts that Cook and Takanishi do not provide any statement that animal testing and whole cell screening is unsatisfactory. Applicant asserts that it is accepted that in vivo results are better predictors of in vivo activity than in vitro. Applicant argues that the NEFA kit is directed to quantitative measurement of fatty acids in serum or blood and is not compatible with the analysis of Bensadoun, Vanio, Cheng and Carroll. Regarding Applicant's assertion that there is no motivation to use a cell-free in vitro for screening inhibitors of LPL, Applicant is directed to a new reference which is cited to meet the newly added limitation of a cell-free in vitro for screening. Pradines-Figueres et al. disclose that there is a systemic underestimation of intracellular LPL activity during its secretion, before or after exposure to heparin. Pradines-Figueres et al. state that this shortcoming of determining LPL activity in an intact cell can be overcome by employing LPL in an in vitro cell-free state. A dramatic enhancement of LPL activity in intracellular activity was induced with a detergent-treated cell lysate. A cell lysate of 3T3-F44A cells, adipose tissue, skeletal muscle cells and cardiac cells (p. 1468, left column top paragraph).

Furthermore, cell lysates can be maintained, or stored indefinitely at an appropriate temperature until use (p. 1469, left column, first paragraph). (It is noted that Bensadoun has been dropped from the rejection.)

Thus, it would have been obvious to employ cell lysates of Cooks preadipocytes. The ordinary artisan would have been motivated to do so because cell lysates provide a more accurate measure of LPL activity that the whole cell method of Cook et al. Furthermore, the ordinary artisan would have realized that it is more convenient to store cell lysates at lowered temperatures until they are needed. The ordinary artisan would have had a reasonable expectation that cell lysates would successfully work in the assay of Cook et al. because Pradines-Figueres et al. demonstrated the reliability of an in vitro cell-free method for assaying LPL.

Regarding Applicant's assertion that Halvorsen is directed to decreasing lipogenesis by administrating linoleic acids (CLA) and that said compound is tested against hormone sensitive lipase (HSL) but not LPL, that Halvorsen teaches assay methods using preadipocytes and that CLA compounds did not diminish lipogensis, Halvorsen was relied upon for disclosure related to vegetable extracts such St. John's wort and other plat extract as can be tested for slimming activity. The ordinary artisan would have been motivated to test the extracts disclosed by the cell-free in vitro LPL assay method of combined references because said extracts have been identified as slimming agents and the ordinary artisan would have known that testing said compounds as LPL inhibitors would be a good indicator of their ability to decrease fat deposits. The ordinary artisan would have had a reasonable expectation that the compounds could be tested by an LPL assay because plants can be made into an extract for easy testing and some plant's such as St. John's wort are known to be slimming agents. Applicant's remaining arguments regarding CLA not relevant.

Responding to Applicant's argument that Cook et al. do not teach a screening method to identify LPL inhibitors for manufacture, Cook et al. teach that the aim of their invention is to discover an effective way to control the body fat and/or body weight of an animal (col. 1, lines 37-40) and they recognize that the modulation of adipocyte LPL is essential to fat accumulation (col. 1, lines 58-59). The

disclosure implicitly meets the limitation of the selection of an inhibitor for manufacture because Cook et al. intend the inhibitors as medical treatments. In order to accomplish this, the successful inhibitors would have to be made or manufactured. Cook et al. meet the limitation of a screening method because they are testing, i.e. screening, multiple compounds by an assay method.

In response to applicant's arguments against the references individually and that the various references are disparate, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The supporting references for the instant rejection are employed to address technical aspects of the assay in the dependent claims. It is not necessary that each of these references be directed to an assay to test for inhibitors that can be used to reduce triglycerides for the purposes if weight loss, improving appearance and so on because the main reference, Cook et al. has been shown to read directly on the intended use of the instant invention. LPL assays are well known in the art and the cited references teach technical aspects of the instant invention not directly taught by Cook et al. For example, Takeda et al. clearly shows that triolein is a suitable substrate for LPL and therefore an obvious substrate choice to for any LPL assay. The NEFA-C kit instructions and Kikuchi et al. were cited to show the commercially available method for FFA that is used by Takeda et al. to assay LPL activity in non-blood assay. Takada et al. also established the wavelength choice and the use of BSA to stabilize triolein. Wagle and Takahashi demonstrated that glycerol stabilizes the triolein substrate and the need to measure LPL activity with a control (Takanishi). Wagle also teaches that medicaments Vanio demonstrates the need for the LPL cofactor. Vanio, Cheng and Takada show other sources of LPL. Thus, Applicants arguments that the references are disparate, that they are not directed to screening for compounds for reducing triglyceride storage in adipocytes and that references are not compatible are not persuasive because Cook is directed to determining inhibitors of inhibiting LPL to control body fat. The ordinary artisan would have realized that there is a great deal of scientific literature that is directed to improving LPL assays. The source of LPL in the various references is not

relevant because LPL from all of the sources catalyze the same reaction and need the same reaction conditions, an emulsion of the substrate, to achieve a successful assay.

Claim 91 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 571-272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Susan Hanley
Patent Examiner
1651